Remarks

Claims 95-98 herein are pending and were previously presented. No new matter is added by the present response.

Prior to responding to the Office Action, Applicants believe it would be of assistance to the Examiner to review the subject matter of the pending claims. Claim 95 is directed to a chimeric neuropeptide Y type Y5 ("NPY5") receptor protein having an amino acid sequence according to amino acid SEQ ID NO: 13, or conservative variants of this sequence in which the C-terminal intracellular domain encoded by nucleotides 1343-1384 of SEQ ID NO: 4 is replaced with that of a neuropeptide Y type Y1 ("NPY1") C-terminal intracellular domain. The chimeric receptor protein of claim 95 exhibits an NPY5 receptor functional response and mediates signal transduction via a G-protein system.

The subject matter of claim 96 is directed to such a protein in which the NPY1 is a human receptor.

The subject matter of claim 97 is directed to such a protein in which the NPY1 C-terminal intracellular domain is encoded by nucleotides 1178-1351 of SEQ ID NO: 1.

The subject matter of claim 98 is a protein in which the C-terminal intracellular domain of NPY5 is replaced with a NPY1 C-terminal intracellular domain resulting in the amino acid sequence of SEQ ID NO: 9.

Claims 95-98 are enabled

The Office Action on pp. 2-5 rejects claims 95-97 under 35 U.S.C. §112 ¶ 1. Applicants here traverse, and assert that the specification would have enabled one of ordinary skill in the art to make and/or use the claims at the time the present application was filed.

One of ordinary skill in the art reading the application at the time it was filed would have been fully enabled to make the chimeric receptor proteins that are the subject matter of claim 95 because, as shown below, the specification as filed includes the following substantial support of the subject matter of claim 95: extensive descriptions of the primary

NPY5 and NPY1 from humans as well as from other genera; methods of making the chimeric receptor proteins; and methods of expressing the chimeric receptor proteins such that it can be assayed for function.

The NPY5 portion of the chimeric receptor protein is constructed from SEQ ID NO: 13 or conservative variants thereof. The specification as filed on p. 6 lines 16-23 (paragraphs 0024 and 0027 as published) provides a description of the primary structure of NPY5 including a description of each of the functional domains. The specification shows that the NPY5 receptor protein has 7 functional domains, and shows the boundaries of each domain. The specification as filed on p. 7 lines 15-32 and p. 8 lines 1-3 (paragraph 0028 as published) further shows the amino acid sequence of each of the domains (SEQ ID NO: 13).

Thus, the specification shows each of the following: the N-terminal extracellular domain from residues 1 (Met) to 50 (Leu); a first transmembrane (TM) domain from residues 51 (Gln) to 71 (Leu); a first intracellular domain from residues 72 (Ile) to 84 (Thr); a second TM domain from residues 85 (Thr) to 105 (Ser); a first extracellular loop domain from residues 106 (Pro) to 125 (His); a third TM domain from residues 126 (Ile) to 146 (Ala); a second intracellular loop domain from residues 147 (Ile) to 167 (Tyr); a fourth TM domain from residues 168 (Phe) to 188 (His); a second extracellular loop domain from residues 188 (Ser) to 220 (Ala); a fifth TM domain from residues 221 (Phe) to 241 (His); a third intracellular loop domain from residues 242 (Thr) to 378 (Tyr); a sixth TM domain from residues 379 (Arg) to 401 (Thr); a third extracellular loop domain from residues 402 (Arg) to 414 (Lys); a seventh TM domain from residues 415 (Leu) to 438 (Leu); and a C-terminal intracellular domain from residues 439 (Asn) to 455 (Met).

This extensive description of the NPY5 protein functional domains, correlated with the portions of the NPY5 amino acid sequences in the specification as filed, would have enabled one of ordinary skill in the art to make the chimeric receptor proteins that are the subject matter of claim 95.

Further, the specification as filed would have enabled the ordinarily skilled artisan to make variants of SEQ ID NO: 9. The specification as filed on p. 8 lines 27-28 (paragraph

0032 as published) cites U.S. patent number 5,985,616 issued November 16, 1999, and incorporates this patent by reference for enabling support with regard to NPY receptor structure and function. U.S. patent number 5,985,616 provides substantial support, more than would have been sufficient to have enabled one of ordinary skill to have made conservative changes in NPY5 protein. Thus, the '616 patent on p. 3 (column 3 lines 66-67 and column 4 lines 1-6) states:

> Some amino acid substitutions are preferably "conservative", with residues replaced with physicochemically similar residues, such as Gly/Ala, Asp/Glu, Val/Ile/Leu, Lys/Arg, Asn/Gln and Phe/Trp/Tyr. Analogs having such conservative substitutions typically retain substantial NPY Y_5 binding activity. Other analogs, which have non-conservative substitutions such as Asn/Glu, Val/Tyr and His/Glu, may substantially lack such activity.

One of ordinary skill in the art of design of protein variants reading at the time the present application was filed the extensive description of structures of SEQ ID NO: 13 correlated with functional domains in the specification, and the '616 patent referenced in the specification, would have been substantially enabled to make conservative variants of SEQ ID NO: 13.

Furthermore, the present specification as filed on p. 6 lines 5-7 (paragraph 0022 as published) states that "sequences of ... Y5 receptors of humans, dogs, mice, guinea pigs, [and] rats....have all been reported and have been published." One of ordinary skill in the art at the time the application was filed would have been enabled to search Genebank for these sequences. A search of the NCBI database under "neuropeptide Y receptor type Y5" with a date limit of January 28, 2001, attached hereto as Appendix **A**, shows 13 published NPY5 sequences, 8 of which are from various mammalian sources. One of ordinary skill in the art at the time the application was filed, reading the extensive structural description of NPY5 provided in the specification as filed on pp. 5-8 (paragraphs 0022, 0024, 0027, 0028, and 0032 as published), which shows the specific metes and bounds of the amino acid sequences of each domain and with knowledge of the published material on NPY5 in other animal genera, would have been fully enabled to choose the residue positions and the amino acids with which to make a large number of functional conservative variants of SEQ ID NO: 13, in order to

practice the subject matter of claim 95.

The Office Action on p. 4 states, "since a single amino acid mutation can change the substrate specificity of a receptor or inactivate it ... [that] it is not predictable as to which amino acids are necessary to maintain the functional characteristics of most receptor proteins." However, claim 95 is in fact directed to functional variants. Applicants assert that characterizing the functional properties of variants is fully enabled by the specification as filed, as shown below. Because claim 95 is directed to a conservative variant of a chimeric receptor protein that exhibits an NPY5 receptor functional response and mediates signal transduction via a G-protein system, a point mutation that eliminates the function is outside of the scope of the claim.

Further, the specification as filed fully enables and makes routine assays that the user of ordinary skill can employ to analyze protein function. See pp. 20-22 of the application as filed (paragraphs 0091-0099 as published). Assays are found in working examples 3-6 on pp. 26-31 of the specification as filed (paragraphs 0116-0131 as published). Thus, Example 3 provides instruction that enables preparation of a baculoviral expression vector, Example 4 provides instruction that enables preparation of purified membranes, Example 5 provides instruction that enables radioligand binding assays for modulators of chimeric receptors, and Example 6 provides instruction that enables functional assays of chimeric NPY receptors. These examples show the user how to measure the extent of binding of the receptor to the cognate ligand, i.e., how to assay function of the claimed protein variants.

Thus, making the chimeric receptor proteins and variants and testing them for proper function was enabled by the application as filed. Applicants assert that the methods for expression and testing function would have been readily recognized by one of skill in the art, at the time the application was filed, in order to determine whether the chimeric receptor proteins that are the subject matter of claim 95 were produced and were functional. The specification as filed on p. 20 lines 24-32 and p. 21 lines 1-6 (paragraph 0095 as published) states:

> An insect system utilizing a baculovirus such as Autographa californica nuclear polyhedrosis virus (AcNPV) can be used to express the recombinant receptors of the invention. The virus grows in insect cells such as Spodoptera

> frugiperda cells (e.g. Sf9). The coding sequence encoding the chimeric NPY receptor of the invention is typically inserted (e.g., ligated) into non-essential regions of the virus (for example into the polyhedrin gene) and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Preferably the successful introduction of the insert will result in inactivation of a viral gene. For example, when targeted into the polyhedrin gene, the successful incorporation of the insert will inactivate that gene and result in production of non-occluded recombinant virus (i.e., virus lacking the proteinaceous coat coded for by the polyhedrin gene). The resulting recombinant viruses are then used to infect insect cells, preferably Spodoptera frugiperda cells, in which the inserted coding sequence is expressed (see, e.g., Smith et al., J. Virol., 46:584, 1983).

The specification as filed on p. 26 lines 20-31 and p. 27 lines 1-22 (paragraphs 0116 and 0117 as published) shows a method for preparing the above expression vector. One of ordinary skill in the art at the time the invention was filed, reading the extensive description of the expression vectors and methods for manufacture thereof provided in the specification on pp. 20-24 and pp. 26-27 (paragraphs 0091-0099, 0116, and 0117), which is the subject matter of claim 95, would have been fully enabled to determine whether one had produced chimeric receptor proteins, and whether those proteins exhibited NPY5 receptor functional response.

Similarly to NPY5, enablement is provided in the specification as filed by extensive structural description of NPY1 domains, and detailed descriptions of NPY1 amino acid sequences, that would have enabled one of ordinary skill in the art to make chimeric receptor proteins and the variants of SEQ ID NO: 9 that are the subject matter of claim 95.

The C-terminal intracellular domain of the chimeric receptor protein of claim 95 was constructed by replacing the NPY5 C-terminal intracellular domain with an NPY1 C-terminal intracellular domain, and conservative variants are enabled by consideration of sequences from other species in the specification as filed. The specification on p. 6 lines 8-15 and p. 8 lines 9-16 (paragraphs 0023, 0029, and 0030 as published) characterizes the Human NPY1 C-terminal amino acid sequence from residues 324 (Asn) to 384 (Ile) of SEQ ID NO: 2. Further, the specification on p. 9 line 14 (0036 as published) shows a rat NPY1 amino acid sequence (SEQ ID NO: 3). A comparison shown below surprisingly shows that these are 100% identical for a

length of 52 residues, and more than 95% identical for 61 residues (only 3 differences indicated in the sequences below in brackets, 58/61 = 95%) at the C-terminal for the Human amino acid sequence (SEQ ID NO: 2) and the rat amino acid sequence (SEQ ID NO: 3):

Human: (324) Asn Lys Asn Phe Gln Arg Asp Leu Gln Phe Phe Phe Asn
Rat: (325) Asn Lys Asn Phe Gln Arg Asp Leu Gln Phe Phe Phe Asn

Human: Phe Cys Asp Phe Arg Ser Arg Asp Asp Asp Tyr Glu Thr Ile Ala Met
Rat: Phe Cys Asp Phe Arg Ser Arg Asp Asp Asp Tyr Glu Thr Ile Ala Met

Human: Ser Thr Met His Thr Asp Val Ser Lys Thr Ser Leu Lys Gln Ala Ser
Rat: Ser Thr Met His Thr Asp Val Ser Lys Thr Ser Leu Lys Gln Ala Ser

Human: Pro Val Ala Phe Lys Lys Ile [Asn] [Asn] Asn Asp [Asp] Asn Glu Lys Ile (384)
Rat: Pro Val Ala Phe Lys Lys Ile [Ser] [Met] Asn Asp [*] Asn Glu Lys Ile (382)

In fact, the specification as filed further enables making variants, as it states that "sequences of Y1.... receptors of humans, dogs, mice, guinea pigs, rats and Y1 receptors of sheep have all been reported and have been published." See p. 6 lines 5-7 (paragraph 0022 as published). One of ordinary skill in the art at the time the application was filed thus directed to availability of this information would have been enabled to obtain these sequences from Genebank. A search of the NCBI database under "neuropeptide Y receptor type Y1", with a date limit of January 28, 2001, is attached hereto as Appendix **B**. This search shows 21 published sequences, 11 of which are various mammalian NPY1 sequences. One of ordinary skill in the art of design of protein variants, comparing the extensive amino acid sequence information available in Genebank with the sequences of NPY1 in the specification on pp. 5-8 (paragraphs 0022, 0023, 0029, 0030, 0035, 0036 as published) with its specific metes and bounds of the amino acid sequence, would have been fully enabled to determine C-terminal intracellular domains of NPY1 that could replace the C-terminal intracellular domain of NPY5 from SEQ ID NO: 4, as is the subject matter of claim 95.

In addition to showing extensive information regarding NPY5 and NPY1, the specification on p. 24 lines 5-31 and p. 25 lines 1-30 (paragraphs 0105-0113 as published)

enables one of ordinary skill in the art to make the chimeric receptor proteins that are the subject matter of claim 95. The specification as filed on p. 25 lines 3-13 (paragraph 0110 as published) provides a detailed description for replacing the C-terminal intracellular domain of an NPY5 receptor protein with the C-terminal intracellular domain of an NPY1 receptor protein. The method shown is not limited to producing SEQ ID NO: 9; rather the method would have enabled one of ordinary skill in the art to produce many different chimeric receptor proteins which are the subject matter of claim 95. For example, the specification on p. 26 lines 1-8 (paragraph 0114 as published) shows that the above method was used to produce canine NPY receptor chimeras (SEQ ID NO: 21), murine NPY receptor chimeras (SEQ ID NO: 22), and rat NPY receptor chimeras (SEQ ID NO: 23). One of ordinary skill in the art, using the methods in the numerous working examples of the specification, would have been fully enabled at the time the present application was filed, to make the chimeric receptor proteins which are the subject matter of claim 95.

Applicants assert that for these reasons, claim 95 is fully enabled. Claims 96 and 97 that depend directly from claim 95 are similarly enabled. Applicants respectfully request that rejection of claims as filed under 35 U.S.C. §112 ¶1 with respect to enablement be withdrawn.

Applicants were in possession of the claimed invention at the time the application was filed

The Office Action on pp. 5-7 rejects claims 95-97 under 35 U.S.C. §112 ¶ 1 with respect to possession of the invention. Applicants here traverse the rejection, and assert that they were in possession of the claimed invention of the pending claims at the time the application was filed.

Applicants respectfully point out that possession of the invention is determined by comparison of Applicants' own written description of the inventive matter, viz., what was included in the specification as filed, compared to the scope of the claims. The Office Action on p. 7 admits that the factors to be considered when evaluating possession of the invention include disclosure of complete or partial structure and methods of making the claimed product or any combination thereof.

Factual analysis shows that working example 1 on pp. 24-25 of the specification as filed (paragraphs 0105-0110 as published) shows how to make a chimeric human NPY5 receptor protein in which the NPY5 C-terminal is replaced with that of a NPY1 C-terminal; the chimera of SEQ ID NO: 9 is an exemplary product of the method of working example 1. Further, working example 2 on p. 26 (paragraphs 0114-0115 as published) shows sequences of similar chimeras for each of mouse (SEQ ID NO: 22) and rat (SEQ ID NO: 24). One of ordinary skill in the art of design of protein variants would have analyzed the amino acid sequences of SEQ ID NO: 22 and SEQ ID NO: 24 in gaining insight for designing conservative variants at residues in comparable amino acid positions in human sequences. These sequences that were provided in the specification as filed support Applicants having been in possession of conservative variants of SEQ ID NO: 9.

In fact, an analysis of the amino acid sequence of human NPY5 (SEQ ID NO: 13) compared to the NPY5 portion of the mouse chimera (SEQ ID NO: 22) shows 84% identity (74 differences in a length of 449, or 375/449 = 84%), between the amino acid sequences of human NPY5 and mouse NPY5. See Appendix **C**. The same analysis of human NPY5 (SEQ ID NO: 13) compared to the NPY5 portion of the rat chimera (SEQ ID NO: 24) shows 87% identity (58 differences or 381/439 = 87%) between the amino acid sequences of human NPY5 and rat NPY5. See Appendix **D**.

One of ordinary skill in the art at the time the application was filed would have recognized that these non-identical residues at comparable positions in sequences of human, mouse, and rat are almost always conservative variants. Mere inspection of the differences at the non-identical residues between human and rat are conservative substitutions, for example, a substitution of one aliphatic amino acid for another (i.e., valine for alanine); and a substitution of one basic amino acid for another (i.e. lysine for arginine). See Appendix **D**. Similarly, one of ordinary skill in the art having knowledge of protein design, comparing the sequences shown in the specification as filed, would have readily grasped that residues in regions of identity were related to function, and the ordinarily skilled artisan would not have introduced variations to the amino acid sequences in the positions having identical residues.

Thus, the ordinarily skilled artisan, using the sequences in the specification as filed, would have understood that conservative amino acid variations as shown through a comparison of these different sequences in Applicants' specification, should be introduced at non-identical positions, and that these changes would not substantially affect function. Function would readily have been determined by the methods provided, as shown in the previous section. These facts show that Applicants were in possession of conservative variants of the claims as pending.

The facts of the present case are different from the facts in the case *Fiddes v. Baird* cited by the Examiner. In the present case, claim 95 is directed to SEQ ID NO: 13, a human chimera, and conservative variants thereof, and the specification as filed shows additional amino acid sequences of mouse and rat chimeras that teach that applications were in possession of conservative variants of SEQ ID NO: 9 as shown above. Further in the present claim 95, the chimeric receptor protein exhibits an NPY5 receptor functional response and mediates signal transduction via a G-protein system.

In the *Fiddes* case the claims at issue encompassed the entire genus of "mammalian" which includes human, yet the written description referred only to a single species, bovine. The *Fiddes* specification did not provide any examples other than bovine to support its claims to the genus of mammalian. In contrast, Applicants' specification shows the amino acid sequences of three mammalian species, including human, rat and mouse chimeras, to support the claims. Therefore, the facts in *Fiddes* are distinct from the present case, rendering *Fiddes* inapposite.

Applicants assert that for the above reasons, Applicants were in possession of the invention to the full scope of claim 95. As Claims 96 and 97 depend directly from claim 95 Applicants were similarly in possession of the invention of these claims. Applicants respectfully request that rejection of claims as filed under 35 U.S.C. §112 ¶1 be withdrawn.

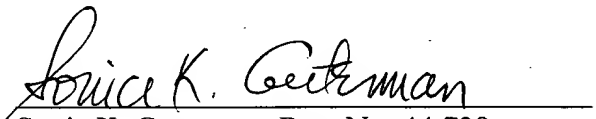
The Office Action on p. 7 objects to claim 98 as being dependent on a rejected base claim. Claim 98 is directed to a chimeric receptor protein according to claim 95 comprising the amino acid sequence of SEQ ID NO: 9. Applicants respectfully assert that for the above

reasons, claim 95 is allowable and the objection to claim 98 can be withdrawn, an action that is respectfully requested.

Summary

On the basis of the foregoing reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative at the telephone number provided.

Respectfully submitted,



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Customer Number 48425

Date: December 7, 2005

APPENDIX A

Appendix A

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1: NP_000896 Reports BLink, Conserved Domains, Links
neuropeptide Y [Homo sapiens]
gi|4505449|ref|NP_000896.1|[4505449]

2: NP_035064 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y1 [Mus musculus]
gi|6754882|ref|NP_035064.1|[6754882]

3: O70342 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor)
gi|13124780|sp|O70342|NPY5R_MOUSE[13124780]

4: O62729 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor) (NPYY5)
gi|3914178|sp|O62729|NPY5R_CANFA[3914178]

5: NP_032945 Reports BLink, Conserved Domains, Links
pancreatic polypeptide receptor 1 [Mus musculus]
gi|31543504|ref|NP_032945.2|[31543504]

6: NP_057917 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y5 [Mus musculus]
gi|7710072|ref|NP_057917.1|[7710072]

7: NP_035065 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y6 [Mus musculus]
gi|6754884|ref|NP_035065.1|[6754884]

8: NP_032757 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y2 [Mus musculus]
gi|6679122|ref|NP_032757.1|[6679122]

9: O97969 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor)
gi|6225788|sp|O97969|NPY5R_PIG[6225788]

☐ **10:** Q63634 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor)
gi|2494994|sp|Q63634|NPY5R_RAT[2494994]

☐ **11:** Q15761 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor) (NPYY5)
gi|2494993|sp|Q15761|NPY5R_HUMAN[2494993]

☐ **12:** Reports BLink, Conserved Domains, Links
AAC17839
neuropeptide Y receptor type 5 [Mus musculus]
gi|3169285|gb|AAC17839.1|[3169285]

☐ **13:** Reports BLink, Conserved Domains, Links
AAC17838
neuropeptide Y receptor type 5 [Canis familiaris]
gi|3169283|gb|AAC17838.1|[3169283]

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APPENDIX B

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☐ **1:** NP_000896 Reports BLink, Conserved Domains, Links
neuropeptide Y [Homo sapiens]
gi|4505449|ref|NP_000896.1|[4505449]

☐ **2:** NP_000901 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y2 [Homo sapiens]
gi|4505447|ref|NP_000901.1|[4505447]

☐ **3:** NP_035064 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y1 [Mus musculus]
gi|6754882|ref|NP_035064.1|[6754882]

☐ **4:** NP_001092 Reports BLink, Conserved Domains, Links
beta actin [Homo sapiens]
gi|4501885|ref|NP_001092.1|[4501885]

☐ **5:** Q04573 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 1 (NPY1-R)
gi|417399|sp|Q04573|NPY1R_MOUSE[417399]

☐ **6:** P25929 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 1 (NPY1-R)
gi|128997|sp|P25929|NPY1R_HUMAN[128997]

☐ **7:** NP_000900 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y1 [Homo sapiens]
gi|4505445|ref|NP_000900.1|[4505445]

☐ **8:** NP_032945 Reports BLink, Conserved Domains, Links
pancreatic polypeptide receptor 1 [Mus musculus]
gi|31543504|ref|NP_032945.2|[31543504]

☐ **9:** NP_057917 Reports BLink, Conserved Domains, Links
neuropeptide Y receptor Y5 [Mus musculus]
gi|7710072|ref|NP_057917.1|[7710072]

☐ **10:** Reports BLink, Conserved Domains, Links
NP_035065
neuropeptide Y receptor Y6 [Mus musculus]
gi|6754884|ref|NP_035065.1|[6754884]

☐ **11:** Reports BLink, Conserved Domains, Links
NP_032757
neuropeptide Y receptor Y2 [Mus musculus]
gi|6679122|ref|NP_032757.1|[6679122]

☐ **12:** Q9WVD0 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 1 (NPY1-R)
gi|9297026|sp|Q9WVD0|NPY1R_CAVPO[9297026]

☐ **13:** P79211 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 2 (NPY2-R) (NPY-Y2 receptor)
gi|3024241|sp|P79211|NPY2R_SHEEP[3024241]

☐ **14:** Q63634 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor)
gi|2494994|sp|Q63634|NPY5R_RAT[2494994]

☐ **15:** Q15761 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5 receptor) (NPYY5)
gi|2494993|sp|Q15761|NPY5R_HUMAN[2494993]

☐ **16:** P34992 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 1 (NPY1-R)
gi|464292|sp|P34992|NPY1R_XENLA[464292]

☐ **17:** Q28602 Reports BLink, Conserved Domains, Links
Neuropeptide Y receptor type 1 (NPY1-R)
gi|3024248|sp|Q28602|NPY1R_SHEEP[3024248]

☐ **18:** Reports BLink, Conserved Domains, Links
AAC26836
neuropeptide Y Y1 receptor [Sus scrofa]
gi|3327382|gb|AAC26836.1|[3327382]

☐ **19:** Reports BLink, Conserved Domains, Links
AAC08046
neuropeptide Y Y1 receptor [Canis familiaris]
gi|2988394|gb|AAC08046.1|[2988394]

☐ **20:** Reports BLink, Conserved Domains, Links
AAB51032
Y1 neuropeptide Y receptor
gi|1480714|gb|AAB51032.1|[1480714]

☐ 21: Reports BLink, Conserved Domains, Links

AAA59947

neuropeptide Y receptor Y1

gi|189285|gb|AAA59947.1|[189285]

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APPENDIX C

Appendix C

Comparison of Human NPY5 (SEQ ID NO: 13) without the C-terminal (last residue is 438) and the NPY5 portion of the mouse chimera (SEQ ID NO: 22) is shown below. Comparison of the sequences was performed by aligning cysteines.

After alignment of the cysteines, these initial sections of the sequences between human and mouse did not have any sections of identity:

Human amino acids (1-24): Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp Glu Tyr Tyr Asn Lys Thr Leu Ala

Mouse amino acids (1-35): Met Glu Val Lys Leu Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala Ser Gln Asn Thr Ala Ser Pro Ala Trp Glu Asp Tyr Arg Gly

The remaining portion of the sequences of human and mouse are compared below:

Human: (25) Thr Glu Asn Asn Thr [Ala] Ala [Thr] Arg Asn [Ser] [Asp] Phe
Mouse: (36) Thr Glu Asn Asn Thr [Ser] Ala [Ala] Arg Asn [Thr] [Ala] Phe

Human: Pro Val Trp [Asp] Asp Tyr [Lys] [Ser] Ser Val Asp Asp Leu Gln Tyr Phe
Mouse: Pro Val Trp [Glu] Asp Tyr [Arg] [Gly] Ser Val Asp Asp Leu Gln Tyr Phe

Human: Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu Gly Phe Met Gly Asn
Mouse: Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu Gly Phe Met Gly Asn

Human: Leu Leu Ile Leu Met Ala [Leu] Met Lys Lys Arg Asn Gln Lys Thr Thr
Mouse: Leu Leu Ile Leu Met Ala [Val] Met Lys Lys Arg Asn Gln Lys Thr Thr

Human: Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser Asp Ile Leu Val Val
Mouse: Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser Asp Ile Leu Val Val

Human: Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val Leu Leu Asp Gln Trp
Mouse: Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val Leu Leu Asp Gln Trp

Human: Met Phe Gly Lys [Val] Met Cys His Ile Met Pro Phe Leu Gln Cys Val
Mouse: Met Phe Gly Lys [Ala] Met Cys His Ile Met Pro Phe Leu Gln Cys Val

Human: Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser Ile Ala Ile Val Arg
Mouse: Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser Ile Ala Ile Val Arg

Human: Tyr His Met Ile Lys His Pro Ile Ser Asn Asn Leu Thr Ala Asn His
Mouse: Tyr His Met Ile Lys His Pro Ile Ser Asn Asn Leu Thr Ala Asn His

Human: Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu Gly Phe Ala Ile Cys
Mouse: Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu Gly Phe Ala Ile Cys

Human: Ser Pro [Leu] Pro Val Phe His Ser Leu Val Glu Leu [Gln] Glu Thr Phe
Mouse: Ser Pro [Phe] Pro Val Phe His Ser Leu Val Glu Leu [Lys] Glu Thr Phe

Human: Gly Ser Ala Leu Leu Ser Ser [Arg] Tyr Leu Cys Val Glu Ser Trp Pro
Mouse: Gly Ser Ala Leu Leu Ser Ser [Lys] Tyr Leu Cys Val Glu Ser Trp Pro

Human: Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser Leu Leu Leu Val Gln
Mouse: Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser Leu Leu Leu Val Gln

Human: Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser His Thr Ser Val Cys
Mouse: Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser His Thr Ser Val Cys

Human: Arg Ser Ile Ser Cys Gly Leu Ser [Asn] Lys Glu Asn Arg Leu Glu Glu
Mouse: Arg Ser Ile Ser Cys Gly Leu Ser [His] Lys Glu Asn Arg Leu Glu Glu

Human: Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser Lys Lys Ser [Gly] [Pro]
Mouse: Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser Lys Lys Ser [Arg] [Asp]

Human: Gln [Val] Lys [Leu] [Ser] [Gly] [Ser] [His] Lys Trp Ser Tyr Ser Phe Ile [Lys]
Mouse: Gln [Ala] Lys [Pro] [Pro] [Ser] [Thr]]Gln] Lys Trp Ser Tyr Ser Phe Ile [Arg]

Human: Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala Cys Val Leu Pro Ala
Mouse: Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala Cys Val Leu Pro Ala

Human: Pro [Glu] [Arg] Pro Ser Gln Glu [Asn] His [Ser] [Arg] [Ile] [Leu] Pro Glu Asn
Mouse: Pro [Ala] [Gly] Pro Ser Gln Glu [Lys] His [Leu] [Thr] [Val] [*] Pro Glu Asn

Human: [Phe] Gly Ser Val Arg Ser Gln Leu Ser [Ser] Ser Ser Lys [Phe] Ile Pro
Mouse: [Pro] Gly Ser Val Arg Ser Gln Leu Ser [Pro] Ser Ser Lys [Val] Ile Pro

Human: Gly Val Pro [Thr] Cys Phe Glu [Ile] Lys Pro Glu Glu [Asn] Ser Asp [Val] [His]
Mouse: Gly Val Pro [Ile] Cys Phe Glu [Val] Lys Pro Glu Glu [Ser] Ser Asp [Ala] [Gln]

Human: Glu [Leu] Arg Val Lys Arg Ser [Val] Thr Arg Ile Lys Lys Arg Ser Arg
Mouse: Glu [Met] Arg Val Lys Arg Ser [Leu] Thr Arg Ile Lys Lys Arg Ser Arg

Human: Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile Leu Val Phe Ala Val Ser
Mouse: Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile Leu Val Phe Ala Val Ser

Human: Trp Met Pro Leu His [Leu] Phe His Val Val Thr Asp Phe Asn Asp Asn
Mouse: Trp Met Pro Leu His [Val] Phe His Val Val Thr Asp Phe Asn Asp Asn

Human: Leu Ile Ser Asn Arg His Phe Lys Leu Val Tyr Cys Ile Cys His Leu
Mouse: Leu Ile Ser Asn Arg His Phe Lys Leu Val Tyr Cys Ile Cys His Leu

Human: Leu Gly Met Met Ser Cys Cys Leu Asn Pro Ile Leu Tyr Gly Phe Leu (438)
Mouse: Leu Gly Met Met Ser Cys Cys Leu Asn Pro Ile Leu Tyr Gly Phe Leu (448)

APPENDIX D

Appendix D

Comparison of Human NPY5 (SEQ ID NO: 13) without the C-terminal (last residue is 438) and the NPY5 portion of the rat chimera (SEQ ID NO: 24) is shown below. Comparison of the sequences was performed by aligning cysteines.

After alignment of the cysteines, these initial sections of the sequences between human and mouse did not have any sections of identity:

Human amino acids (1-6): Met Ser Phe Tyr Ser Lys

Rat amino acids (1-7): Met Asp Val Leu Phe Phe His

The remaining portion of the sequences of human and mouse are compared below:

Human: (7) Gln Asp [Tyr] [Asn] Met [Asp] [Leu] [Glu] Leu
Rat: (8) Gln Asp [Ser] [Ser] Met [Glu] [Phe] [Lys] Leu

Human: [Asp] Glu [Tyr] [Tyr] Asn Lys Thr [Leu] [Ala] Thr Glu Asn Asn Thr Ala Ala
Rat: [Glu] Glu [His] [Phe] Asn Lys Thr [Phe] [Val] Thr Glu Asn Asn Thr Ala Ala

Human: [Thr] Arg Asn [Ser] [Asp] Phe Pro [Val] Trp [Asp] Asp Tyr [Lys] [Ser] Ser Val
Rat: [Ala] Arg Asn [Ala] [Ala] Phe Pro [Ala] Trp [Glu] Asp Tyr [Arg] [Gly] Ser Val

Human: Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu
Rat: Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu

Human: Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala [Leu] Met Lys Lys
Rat: Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala [Val] Met Lys Lys

Human: Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
Rat: Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe

Human: Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser
Rat: Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser

Human: Val Leu Leu Asp Gln Trp Met Phe Gly Lys [Val] Met Cys His Ile Met
Rat: Val Leu Leu Asp Gln Trp Met Phe Gly Lys [Ala] Met Cys His Ile Met

Human: Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile
Rat: Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile

Human: Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn
Rat: Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn

Human: Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr
Rat: Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr

Human: Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val
Rat: Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val

Human: Glu Leu [Gln] Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser [Arg] Tyr Leu
Rat: Glu Leu [Lys] Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser [Lys] Tyr Leu

Human: Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile
Rat: Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile

Human: Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val
Rat: Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val

Human: Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser [Asn] Lys
Rat: Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser [His] Lys

Human: Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu [His] Pro
Rat: Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu [Gln] Pro

Human: Ser Lys Lys Ser [Gly] [Pro] Gln [Val] Lys [Leu] [Ser] [Gly] [Ser] [His] Lys Trp
Rat: Ser Lys Lys Ser [Arg] [Asn] Gln [Ala] Lys [Thr] [Pro] [Ser] [Thr] [Gln] Lys Trp

Human: Ser Tyr Ser Phe Ile [Lys] Lys His Arg Arg Arg Tyr Ser Lys Lys Thr
Rat: Ser Tyr Ser Phe Ile [Arg] Lys His Arg Arg Arg Tyr Ser Lys Lys Thr

Human: Ala Cys Val Leu Pro Ala Pro [Glu] [Arg] Pro Ser Gln [Glu] [Asn] His [Ser]
Rat: Ala Cys Val Leu Pro Ala Pro [Ala] [Gly] Pro Ser Gln [Gly] [Lys] His [Leu]

Human: [Arg] [Ile] [Leu] Pro Glu Asn [Phe] [Gly] Ser Val Arg Ser Gln Leu Ser [Ser] Ser
Rat: [Ala] [Val] [*] Pro Glu Asn [Pro] [Ala] Ser Val Arg Ser Gln Leu Ser [Pro] Ser

Human: Ser Lys [Phe] Ile Pro Gly Val Pro [Thr] Cys Phe Glu [Ile] Lys Pro Glu
Rat: Ser Lys [Val] Ile Pro Gly Val Pro [Ile] Cys Phe Glu [Val] Lys Pro Glu

Human: Glu [Asn] Ser Asp [Val] His Glu [Leu] Arg Val Lys Arg Ser [Val] Thr Arg
Rat: Glu [Ser] Ser Asp [Ala] His Glu [Met] Arg Val Lys Arg Ser [Ile] Thr Arg

Human: Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
Rat: Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile

Human: Leu Val Phe Ala Val Ser Trp Met Pro Leu His [Leu] Phe His Val Val
Rat: Leu Val Phe Ala Val Ser Trp Met Pro Leu His [Val] Phe His Val Val

Human: Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
Rat: Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val

Human: Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
Rat: Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro

Human: Ile Leu Tyr Gly Phe Leu (438)
Rat: Ile Leu Tyr Gly Phe Leu (438)